Journal of the American College of Cardiology Vol. 49, No. 18, 2007

ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.01.075

Depression Is a Risk Factor for Mortality After Myocardial Infarction

Fact or Artifact?

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Objectives This study sought to investigate the long-term impact of depression on cardiac mortality after myocardial infarction (MI) and to assess whether the timing of depression influences the findings.

Background Previous studies have shown that depression increases the risk of cardiac death after MI, although some studies with robust methodology have failed to show this effect. Clinical trials of depression treatments have failed to improve mortality. Until the relationship between depression and post-MI mortality is understood fully, clinical trials aimed at reducing mortality by treating depression remain premature.

Methods We recruited 588 subjects after MI and followed up their cases for up to 8 years. Patients underwent detailed assessments of cardiac status, conventional cardiac risk factors, and noncardiac illness at baseline. Depression was assessed for the period immediately preceding MI and at 12 months after MI, using a standardized questionnaire and a research interview. At follow-up, the mortality status, cause, and date of death were recorded for 587 subjects using population records.

Results Multivariate predictors of cardiac death included older age (hazard ratio [HR] = 1.04, p = 0.007), previous angina (HR = 1.8, p = 0.03), previous MIs (HR = 1.6, p = 0.004), Killip class (HR = 1.8, p = 0.005), beta-blockers (HR = 0.5, p = 0.023), and angiotensin-converting enzyme inhibitors (HR = 0.6, p = 0.047) prescribed on discharge. Depression was not associated with cardiac mortality, whether detected immediately before MI (p = 0.48), 12 months after MI (p = 0.27), or at both time points (p = 0.97).

Conclusions The association between depression and post-MI mortality is complex, possibly being limited to depression immediately after MI. Defining the window when intervention for depression might benefit survival is crucial for the design of future trials. (J Am Coll Cardiol 2007;49:1834–40) © 2007 by the American College of Cardiology Foundation

Two recent systematic reviews have shown that, in people with established coronary heart disease, depression predicts an approximate 2-fold increase in all-cause mortality and cardiac mortality (1,2). Despite the consistency of the findings in these reviews, it remains unclear why a number of individual studies with robust methodologies have failed to show an adverse effect of depression on mortality (3–7). Furthermore, psychological interventions have failed to show a reduction in mortality, which would be expected if depression caused an increase in mortality (8). The conflicting results of previous studies may be attributable to the way depression is measured, because different measures may be sensitive to different dimensions of depression, or duration of follow-up (2), although variation in timing of the assessments and variable attempts to control for the confounding effect of severity of heart disease may be responsible for the heterogeneity (9). Until the causes of this heterogeneity can be firmly established, however, the extent to which depression increases mortality in coronary heart disease remains uncertain (10–13).

We report here the findings of a prospective cohort study to examine the effects of depression on cardiac mortality after myocardial infarction (MI). Because there is strong evidence showing that depression is a risk factor for incident coronary heart disease (14–16), our first assessment of depression concerned the period immediately before MI. The second assessment was 12 months after MI, and cardiac mortality was assessed over a 7-year period after MI. We used both a semi-standardized research interview and a

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Manuscript received October 13, 2006; revised manuscript received January 22, 2007, accepted January 28, 2007.

validated questionnaire to measure depression, because type of measure may affect the results (1,17), and we adjusted our results both for severity of MI and other recognized risk factors for cardiac disease. The exceptional characteristic of our study was that, by using population records, we were able to follow up more than 99% of subjects for up to 8 years and obtain cause of death as recorded on death certificate. We tested the hypothesis that depression occurring before the MI, 12 months after MI, and at both time points would be associated with increased mortality, after controlling for demographic factors, conventional cardiac risks, and severity of index MI.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CABG = coronary artery bypass graft
CI = confidence interval
CPK = creatine phosphokinase
HADS = Hospital Anxiety and Depression Scale
MI = myocardial infarction

Methods

Sample. Consecutive patients with suspected MI admitted to 4 inner-city hospitals between October 1997 and November 1999 were screened. Subjects were included if they met World Health Organization criteria for MI during their hospital admission (18). Two of the following were required: 1) history of typical chest pain; 2) characteristic electrocardiogram changes; and 3) a serial increase in creatine phosphokinase (CPK) to greater than twice normal limits. Patients were excluded if they: 1) were too unwell to complete the assessment even with assistance from the researcher; 2) suffered from a serious comorbid medical condition; 3) were insufficiently fluent in English; 4) were more than 80 years of age; and 5) lived outside the catchment areas of the hospitals used for recruitment of subjects.

Baseline assessments. Suitable subjects were assessed on average 3.6 (standard deviation 2.1) days after the MI. We recorded: 1) demographic factors including age, gender, ethnicity, marital status, and years of education; 2) smoking and use of illegal drugs; and 3) past medical history, including previous or family history of cardiovascular disease, and past psychiatric history (emotional disorder treated by a general practitioner, psychiatrist, psychologist, or psychotherapist). Socioeconomic status was recorded using the criteria of Goldthorpe and Hope (19), based on current or past employment of subject or partner. Severity of angina before MI was assessed using the Rose Angina Questionnaire (20).

Severity of the index MI was assessed using 4 measures:

1. Killip class (21), a brief scale rating left ventricular function based on the presence of pulmonary rales, S3 gallop, and peripheral hypoperfusion. High scores represent worse left ventricular function. This information was taken from the hospital records, which were based on the findings of physical examinations performed by a cardiologist.
2. CPK values, recorded over the 3 days after MI.
3. Medication on discharge from hospital.
4. Echocardiogram assessments of cardiac output were performed on a substantial subgroup of subjects (n = 379), with cardiac outputs categorized as poor (<30%), moderate (30% to 50%), and good (>50%).

Blood pressure on admission, any serious cardiac complications (further MI/extension of MI, cardiac arrest) and coronary artery bypass graft (CABG) performed during index admission were recorded from the medical records.

Social support was assessed in terms of whether subjects had a close confidant, i.e., someone with whom the subject had regular contact (at least once per month) and with whom she or he could share sensitive personal information and gain support (3).

Anxiety and depression were assessed primarily using the Hospital Anxiety and Depression Scale (HADS) (22). At baseline assessment subjects were instructed to complete the HADS questionnaire to reflect their mental state in the week preceding the MI. Because participants were seen usually on the third or fourth day after their MI, this represented 4 to 11 days before our assessment. This differs slightly from the conventional use of the HADS, in which subjects are instructed to report how they have been feeling in the 7 days immediately preceding the assessment. We have reported previously that individuals were able to differentiate their pre-MI mood from that in the immediate aftermath of their MI (3).

To validate the use of the HADS in this way, we administered to 313 patients the Schedule for Clinical Assessment in Neuropsychiatry (23), a semistructured research interview designed to assess psychiatric symptoms retrospectively. In this way we ascertained whether individuals met Internation Classification of Diseases (ICD)-10 criteria for depression before their MI. We then determined the cutoff for the HADS (total combined anxiety and depression score of 17 or above), which provided the best sensitivity (87.7%) and specificity (84.7%) to diagnose depressive disorder (3).

We also assessed depression using the HADS questionnaire at 12 months after MI (n = 440). On this occasion the HADS was completed conventionally.

Outcome. Follow-up information was obtained on 587 of 588 subjects from the Office of National Statistics. The main outcome for this study was cardiac mortality as determined from death certificate diagnoses obtained from the Office of National Statistics.

Statistical analysis. To assess the impact of depression on cardiac mortality, we identified individuals who fulfilled criteria for depression before MI, 12 months after MI, and at both times. We used these 3 measures of depression as predictors in 3 separate analyses. Kaplan-Meier survival analysis was performed and survival in depressed and nondepressed subjects was compared using log-rank (Mantel-Cox) analysis.

We used Cox regression to examine the association of depression with time to cardiac death, controlling for demographic and medical variables. Baseline demographic

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Table 1 Comparison of Baseline Characteristics of Patients Who Had Cardiac Death Versus Those Who Survived

	Alive*	Cardiac Death*	p Value†
Number of subjects	449 (85%)	78 (15%)	
Demographic details			
Age (yrs)	58.1 (10.9)	65.6 (9.4)	<0.0005
Gender			
Male	315 (70.2%)	60 (76.9%)	0.28
Female	134 (29.8%)	18 (23.1%)	
Ethnicity			
Caucasian	422 (94.0%)	76 (97.4%)	0.58
Asian	18 (4.0%)	1 (1.3%)	
Afro-Caribbean	6 (1.3%)	1 (1.3%)	
Other	3 (0.7%)	0	
Marital status			
Single	45 (10.0%)	6 (7.7%)	0.16
Married/cohabiting	296 (65.9%)	45 (57.7%)	
Widowed	57 (12.7%)	17 (21.8%)	
Divorced/separated	51 (11.4%)	10 (12.8%)	
Close confidant (n = 507)	371 (85.7%)	59 (79.7%)	0.22
Educated to GCSE‡ or more	130 (29%)	10 (12.8%)	0.002
Job class§			
Class 1–21	193 (44.7)	31 (40.8)	0.62
Class 22–35	239 (55.3)	45 (59.2)	
Comorbid medical factors			
Gastrointestinal problems	58 (12.9%)	8 (10.3%)	0.58
Respiratory problems	62 (13.8%)	18 (23.1%)	0.041
Joint problems	128 (28.5%)	19 (24.4%)	0.50
Illegal drug use (n = 523)	22 (4.9%)	0 (0%)	0.058
Conventional coronary risks			
Family history of MI (n = 506)	261 (59.9%)	36 (51.4%)	0.19
History of diabetes	35 (7.8%)	16 (20.5%)	0.001
History of hypertension	131 (29.2%)	28 (35.9%)	0.23
History of angina	81 (18.0%)	36 (46.2%)	<0.0005
Cholesterol on admission (n = 512)	6.0 (1.3)	5.5 (1.1)	0.008
Smoking history			
Never smoked	81 (18.0%)	15 (19.7%)	0.042
Current smoker	237 (52.8%)	29 (38.2%)	
Past smoker	131 (29.2%)	32 (42.1%)	
Number of previous MIs			
0	397 (88.4%)	48 (61.5%)	<0.0005
1	44 (9.8%)	19 (24.4%)	
2	8 (1.8%)	6 (7.7%)	
3	0	3 (3.8%)	
4	0	2 (2.6%)	
Previous CABG (n = 237)	10 (5.3%)	9/47 (19.1%)	0.004
Severity of angina (Rose)			
Moderate	49 (62.0)	23 (74.2)	
Severe	30 (38.0)	8 (25.8)	0.27
Blood pressure on admission (n = 512)			
Diastolic	69.7 (12.8)	70.8 (13.0)	0.49
Systolic¶	120.7 (16.3)	121.0 (20.8)	0.89
Severity of MI			
Killip class = 1	335 (74.8%)	31 (40.3%)	<0.0005
Killip class = 2	103 (23.0%)	32 (41.6%)	
Killip class = 3	10 (2.2%)	14 (18.2%)	
Cardiac output echocardiogram			
>50%	151 (50.3%)	3 (7.0%)	<0.0005
30% to 50%	137 (45.7%)	29 (67.4%)	
<30%	12 (4.0%)	11 (25.6%)	

Continued on next page

Table 1 Continued

	Alive*	Cardiac Death*	p Value†
CPK‖			
1st sample (n = 521)	593 (923)	618 (749)	0.83
2nd sample (n = 524)	1,240 (1,213)	1,356 (1,271)	0.44
3rd sample (n = 475)	927 (1,099)	1,073 (1,424)	0.32
Thrombolysis (n = 524)	331 (73.9%)	47 (61.8%)	0.018
Severe cardiac complications during index admission (n = 318)	32 (12.3%)	9 (15.5%)	0.52
Coronary artery bypass graft during index admission (n = 520)	9 (2.0%)	1 (1.3%)	1.0
Discharge medication			
Aspirin (n = 510)	423 (95.7%)	61 (89.7%)	0.067
Beta-blockers (n = 510)	286 (64.7%)	21 (30.9%)	<0.0005
Calcium channel blockers (n = 510)	85 (19.2%)	18 (26.5%)	0.19
ACE inhibitors (n = 509)	186 (42.2%)	36 (52.9%)	0.12
Nitrates (n = 509)	273 (61.9%)	43 (63.2%)	0.89
Cholesterol-lowering statins (n = 509)	335 (76%)	44 (64.7%)	0.053
Diuretics (n = 508)	65 (14.8%)	31 (45.6%)	<0.0005
Antidepressants (n = 507)	19 (4.3%)	2 (2.9%)	1.0
Psychosocial factors			
Past psychiatric history (n = 526)	160 (35.6%)	24 (31.2%)	0.52
Total HADS	10.9 (7.9)	11.2 (7.4)	0.79
Depressed (HADS total ≥17)	108 (24.1)	17 (21.8)	0.77
Hostility score (n = 490)	1.82 (1.3)	1.83 (1.3)	0.96
Aggression score (n = 489)	4.0 (1.9)	4.0 (2.0)	0.88

*Figures presented are either mean (standard deviation) for continuous variables or number of subjects (%) for categorical variables. Data are presented on the total sample of 527 subjects who were alive at final follow-up or who had died of cardiac causes. Where data are missing, number of subjects on whom data were included in analysis is detailed in parentheses after the variable names. †Significance from chi-square test, Fisher exact test, or *t* test, as appropriate. ‡GCSE refers to General Certificate of Secondary Education (equivalent to 12 years of education). §Job class 1–21 reflects higher socioeconomic status, 22–35 reflects lower status. ¶Unequal variance version of the *t* test was used. ‖Comparisons made using the Mann-Whitney *U* test in view of degree of nonnormality of distribution of variables; p = 0.052 (1st sample), 0.64 (2nd sample), and 0.68 (3rd sample).

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; CPK = creatine phosphokinase; HADS = Hospital Anxiety and Depression Scale; MI = myocardial infarction.

and physical variables that were significantly ($p < 0.05$) or nearly significantly ($p < 0.2$) associated with cardiac death, together with any other demographic and physical variables that have been associated with cardiovascular disease in previous research, (e.g., socioeconomic status and medication on discharge) were entered as independent variables.

The following covariates were included in the regression analysis using forced entry: age, gender, marital status, years of education, socioeconomic status, history of comorbid medical problems (diabetes, respiratory, abdominal, or musculoskeletal problems), family history of MI, number of previous MIs, history of prior angina or CABG, cholesterol, smoking, Killip class, CPK level on admission, cardiac complications during index admission, thrombolysis on index admission, medication on discharge (aspirin, beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, cholesterol lowering statins, diuretics). Depression or social support were entered in a separate block to test the significance of adding these variables, after adjusting for all possible confounding variables. We repeated the analysis 3 times, entering depression measured at different time points (depression at baseline, depression at 12 months, and depression that persisted from baseline to 12 months).

For the multivariate analysis, missing values were replaced using mean substitution. For 2 variables the extent of missing data was substantial (history of CABG before MI, n = 237; left ventricular ejection fraction, n = 379). These variables were excluded from the main analysis, although subsequent analyses showed that the result for depression was stable whether these variables were included with mean substitution or whether the analysis was limited to those subjects for whom complete data on this item were recorded. For brevity only the results with these variables excluded are presented.

This study complied with the Declaration of Helsinki. Full ethical permission was granted by Local Research Ethical Committees (ethics application numbers: NOR/98/021, CM/97/090, 98090).

Results

The baseline characteristics of our subjects have been reported previously (3), so only the main features of our sample are reported here.

Of the 654 subjects that fulfilled our inclusion and exclusion criteria, 588 (90%) subjects completed baseline assessments. The mean age of the sample was 60.0 years (SD = 11.1); 414 (70.4%) were male. Four hundred and ninety-two subjects (84%) were admitted after their first MI, 74 with their second, 17 with their third, 3 with their fourth, and 2 with their fifth; 140 (23.8%) had depressive disorder (HADS score ≥17).

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Of the 588 completing baseline assessments, 587 were traced at follow-up. Mean duration of follow-up was 6.75 years (range 6 to 8 years). Of the 587 on whom survival data were available, 78 (13.3%) subjects had suffered death caused by cardiac cause; 60 (10.2%) subjects had died of a noncardiac cause.

Comparison of the 78 subjects dying of cardiac causes with 449 subjects alive at the time of final assessment is presented in Table 1. Mortality was associated with subjects' age, educational status, presence of comorbid respiratory problems, diabetes, previous cardiovascular disease (angina, MI, or CABG), history of smoking, high cholesterol, more severe MI (high Killip class or low left ventricular ejection fraction), whether thrombolysis was used, and drugs prescribed on discharge from hospital (beta-blockers and diuretics).

There was no significant difference in survival between those with depression (HADS total score ≥17) in the week preceding MI (mean survival 89.2 months, 95% confidence interval [CI] 84.7 to 93.8) and those without (mean survival 89.9 months, 95% CI 87.4 to 92.4, log rank [Mantel-Cox] chi-square 0.10, p = 0.75) (Fig. 1).

For the subgroup (n = 313) of subjects undergoing the semistandardized research interview, those diagnosed as depressed (ICD-10 criteria) showed similar survival to those who were not depressed (mean survivals 95.4 months [95% CI 91.2 to 99.6] and 92.0 months [95% CI 89.1 to 95.0], respectively, log rank p = 0.12). Those without a close confidant showed similar mortality to those who reported having a confidant (mean survival 85.3 months [95% CI 78.7 to 91.9] and 90.8 months [95% CI 88.5 to 93.1], respectively, log rank p = 0.15).

For the subgroup who returned HADS postal assessments at 12 months (n = 440, 81% of those alive at 12 months), depressed subjects showed no difference in survival compared with the nondepressed (mean survival 94.1 months [95% CI 91.0 to 97.2] and 96.3 [95% CI 94.7 to 97.9], respectively, log rank p = 0.66). Among the 53 patients who were depressed at both baseline and 12 months (HADS total score ≥17) there were no cardiac-related deaths during the following 6 years, compared with 32 cardiac deaths in the 387 nondepressed patients (8.3%). Those depressed at baseline and at 12 months had significantly better survival than those who were not depressed (log rank p = 0.031).

On Cox regression, predictors of mortality during the follow-up period were older age, history of angina, number of previous MIs, and Killip class after index MI. Predictors of survival were whether individuals were prescribed beta-blockers or ACE inhibitors on discharge (Table 2).

Depression failed to contribute to this model whether cases of depression were defined using HADS score ≥17 (n = 587, p = 0.48), ICD criteria (n = 313, p = 0.09)*, depression at 12-month follow-up (HADS ≥17; n = 440, p = 0.27), or depression at both baseline and 12 months (n = 440, p = 0.97). Furthermore, having a close confidant failed to predict survival (n = 587, p = 0.51), and there was no significant interaction between having a close confidant and HADS depression (p = 0.49).

A retrospective power calculation showed that, given our population size and the prevalence of depression, our study had 80% power to detect a hazard ratio of 1.42 at the level of significance p = 0.05. This would equate to a mortality rate of 24.5% in the depressed if the mortality rate in the nondepressed remained the same (13.6%).

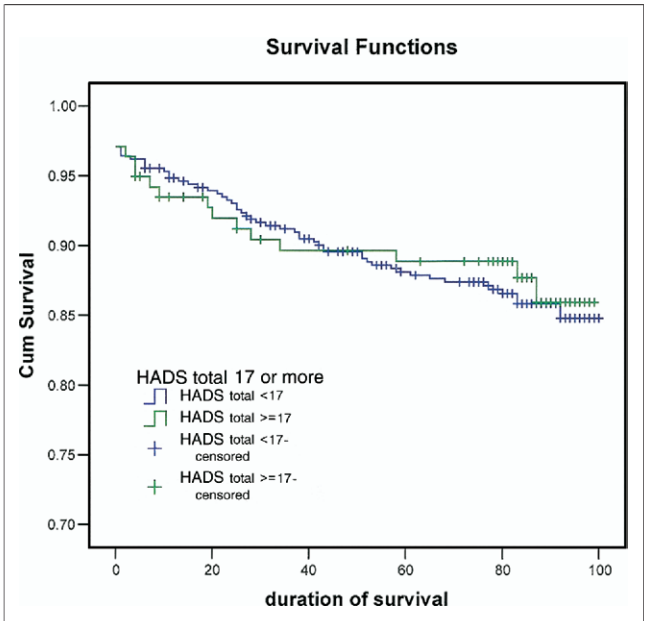

Figure 1 Survival Functions

Survival curves for depressed and nondepressed patients (Hospital Anxiety and Depression Scale [HADS] total score ≥17 in the week before myocardial infarction). Cum = cumulative.

Discussion

In a fairly large cohort of people admitted to the hospital after MI, we did not find that depression predicted a subsequent increase in cardiac mortality, whether we considered depression before MI, depression 12 months after MI, or depression that was present at both times. Cardiac mortality was predicted by greater age, history of angina and previous MI, and cardiac failure during admission. Survival was predicted by prescription of beta-blockers and ACE inhibitors on discharge.

The major strength of our study was our ability to trace 587 of the original 588 subjects for up to 8 years after MI and to obtain details of cause of death. We assessed accurately depression at 2 time points and analyzed separately those who were depressed at both times. We were able also to adjust for a wide range of psychosocial factors and the cardiac status of our patients after their MI. The major weakness relates to comparison with other studies—we did not measure depression in the weeks immediately after MI as others have done.

*Regression coefficient = −1.1 indicating a trend for ICD-10 depression to protect against cardiac mortality.

Table 2 Cox Regression Investigating Predictors of Survival After MI

	Regression Coefficient (SE)	p Value	Hazard Ratio	95% CI for Hazard Ratio
Age	0.04 (0.015)	0.007	1.04	1.01–1.07
Pre-MI angina	0.59 (0.28)	0.033	1.81	1.05–3.13
Number of previous MIs	0.48 (0.17)	0.004	1.61	1.17–2.23
Killip class	0.57 (0.20)	0.005	1.76	1.18–2.62
Beta-blockers on discharge	−0.66 (0.29)	0.023	0.52	0.29–0.91
ACE inhibitors on discharge	−0.55 (0.28)	0.047	0.58	0.34–0.99
HADS score ≥17	−0.22 (0.31)	0.48	0.81	0.44–1.47

CI = confidence interval; other abbreviations as in Table 1.

Our findings, that depression is not an independent risk factor for cardiac mortality after MI, differ from those of a number of other studies (1,2). Although this difference in study findings could be explained by the fact that we recorded depression immediately before and/or 12 months after MI but did not assess depression immediately after MI, some other studies that have recorded depression immediately after MI have still failed to detect an effect of depression on mortality (4–7). This suggests that, although timing of the depression assessment may have been a contributory factor in explaining why our findings differed from those of other studies, it does not explain completely the heterogeneity of findings in this research overall.

We chose to measure depression immediately preceding MI because there is good evidence showing that depression preceding MI is associated with incident coronary heart disease (14–16) and cardiac death (24–26). We assumed that depression present before the MI, especially that which is chronic, would be a risk factor for poor outcome after MI also, because it is associated with persistent social difficulties and heavy smoking (27,28). In addition, our patients were only in the hospital a few days and we did not regard the fluctuating distress reported by patients immediately after an MI as true depressive disorder (28). Such distress is transient in many (28,29), whereas we were interested in the persisting symptoms of depressed mood associated with altered patterns of sleep, appetite, and concentration that amounted to depressive illness, which we assumed would be more likely to be associated with cardiac problems (26,30). Our patients had no difficulty reporting these depressive symptoms for the week preceding MI. Although our methods have highlighted the complexities in the association between depression and outcome after MI, in retrospect it would have been useful to have recorded depression for the 2 to 4 weeks immediately after MI also, to facilitate comparison of our study with others.

Our negative finding for depression preceding MI is consistent with the only other study, by Lesperance et al. (31), to have measured depression in the period immediately before MI and examined its impact on subsequent mortality. Unlike another study by the same group, we did not find that depression 12 months after MI predicted subsequent mortality, although the impact of 12-month depression on mortality in the Lesperance study did become nonsignificant once the effects of baseline depression were controlled (32).

It remains possible that it is depressive disorder or even transient depressive symptoms (i.e., acute distress) developing in the immediate post-MI period that are particularly cardiotoxic (33). Such acute distress is a recognized precipitant of MI (34), and thus is a likely risk factor of further acute coronary events after MI, possibly because of its effect on autonomic tone at a time when the myocardium is very sensitive, thus leading to arrhythmias (35). This would be consistent with the observation that post-MI depressive symptoms in the days after MI are particularly associated with sudden death in individuals showing a high number of premature ventricular contractions, suggesting that arrhythmias are the most likely cause of death (17). If the relationship between depression and mortality is confined to depression immediately after MI, then this has important implications for intervention trials; for example, the ENRICHD (Enhancing Recovery in Coronary Heart Disease Patients) trial recruited patients within 28 days after their MI.

Despite our negative finding, we do not conclude that depression before and after MI is unimportant. We have previously shown that depression around the time of MI is a potent predictor of impairment in health-related quality of life (36). Because mortality is declining as an outcome after MI and there is a trend for a reduction in the effect of depression on mortality (2), future intervention studies might wish to consider quality of life as their primary outcome. Studies will be smaller in size, and findings are likely to generalizable to a greater proportion of people with coronary heart disease.

Our findings highlight the complexity of the association between depression and coronary heart disease. One possible reason for this is the suggestion that depression leads to poor outcome through different mechanisms at different times (34). On the one hand, depression is associated with incident heart disease after controlling for other risk factors such as smoking (in otherwise healthy individuals). The latency of this effect seems to be years rather than weeks or months, suggesting that depression plays a part in increased atherogenesis through physiological and/or behavioral pathways; this effect is possibly greater in those who have received treatment for depression (37,38). Depression and acute distress in the period immediately after MI appear to

be associated with cardiac mortality, although the time course is much shorter (weeks to months) and the risks are greatest in those with high risks of arrhythmias (17). Outside this immediate post-MI period, the adverse impact of depression diminishes. It is likely that the risks of arrhythmia will be lower once the myocardium has recovered and that any long-term pro-atheromatous effects of depression are moderated by treatments for the heart disease.

Future observational studies should consider carefully the timing of onset of depression and whether any specific symptoms or dimensions of depression are particularly cardiotoxic to identify subgroups that are most likely to benefit from treatment. The importance of understanding these relationships more exactly lies in the need to design with greater precision further intervention studies to test whether improved depression leads to reduced mortality (29).

Acknowledgment

The authors acknowledge the help of Amina Jamil in the collection of follow-up data.

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